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Nonthermal Biological Effects of Microwaves: Current Knowledge, Further Perspective, and Urgent Needs

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The aim of this article is to present an overview of diverse biological effects of nonthermal microwaves (NT MWs) and complex dependence of these effects on various physical and biological parameters. Besides well-known dependencies on frequency and modulation, the available data suggest dependencies of the NT MW effects on intermittence and coherence time of exposure, polarization, genotype, gender, physiological and individual factors, static magnetic filed, electromagnetic stray field, cell density during of exposure, and indicate that duration of exposure may be more important than PD for the NT MW effects. Further evaluation of these dependencies are needed for understanding the mechanisms by which NT MWs affect biological systems, eventual poor reproducibility of the NT MW effects, planning in vivo and epidemiological studies, developing medical treatments, setting safety standards, and minimizing the adverse effects of MWs from mobile communication.

Keywords DNA damage; Genome; Mobile (cellular) phones; Modulation; Nonthermal microwaves; Polarization; Stress response.

Introduction

Electromagnetic exposures vary in many parameters: power (specific absorption rate, incident power density), wavelength/frequency, near field/far field, overall duration and intermittence of exposure (continuous, interrupted), acute and chronic exposures, polarization (linear, circular) continues wave (CW) and pulsed fields (pulse repetition rate, pulse width or duty cycle, pulse shape, pulse to average power, etc.), modulation (amplitude, frequency, phase, complex), static magnetic field (SMF) and electromagnetic stray field at the place of exposure. With increased absorption of energy, so-called thermal effects of microwaves (MWs) usually are

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observed that deal with MW-induced heating. Specific absorption rate (SAR) or power density (PD) is a main determinate for the thermal MW effects. Many other physical parameters of exposure may be important for so-called nonthermal (NT) biological effects, which are induced by MWs at intensities well below any heating [1–12]. An important question how these physical parameters should be taken into account in safety standards.

Most often, the current safety standards are based on thermal effects of MWs obtained in short-term (acute) exposures. In some countries, such as Russia, the NT MW effects, especially those induced during prolonged (chronic) exposures, are accepted and taken into account for establishment of the national safety standards [7, 8, 13]. It should be stressed, that in contrast to the International Commission for Non-Ionizing Radiation Protection (ICNIRP) safety standards, which are based on the acute effects of thermal MWs, the former Soviet standards and the current Russian standards, adopted by the Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP), are based on the experimental data from chronic (up to 4 month) exposures of animals to MWs at various physical parameters including intensity, frequency and modulation [7, 8, 13]. Since establishment of the current safety standards, the situation with exposure of general population to MWs has been changed significantly. Nowadays, most part of population is chronically exposed to MW signals from various sources including mobile phones and base stations. These exposures are characterized by very low intensities, varieties of signals, and long-term durations of exposure comparable with lifespan. So far, the "dose" (accumulated absorbed energy that is measured in radiobiology as the dose rate multiplied by the exposure time) is not accepted for MW exposures and SAR or PD is used for guidelines. The degree to which SAR/PD can be applied nowadays to NT MW chronic exposures is not known and the current state of research demands reevaluation of the safety standards [13].

There are 2 main approaches to treat numerous data regarding the NT MW effects. The first is based on the consideration of these effects dependent on various physical parameters and biological variables as consistently described in many experimental studies and will be partially reviewed in this article. The second approach is based on neglecting or minimizing such experimentally observed dependencies based on the current state of physical science that is insufficient for comprehensive explanation of the NT MWs effects in frames of theoretical physics. As a result of such various treatments of the data on the NT MW biological effects, the safety standards significantly vary between countries, up to 1,000 times.

The literature on the NT MW effects is very broad and this article is not intended to be a comprehensive review of the literature. There are 4 lines of evidence for NT MW effects:

(1) altered cell responses in laboratory in vitro studies and results of chronic exposures in vivo studies (this review);
(2) medical application of NT MWs (former Soviet Union countries) [4, 6, 14, 15];
(3) hypersensitivity to electromagnetic fields (EMFs) [16];
(4) epidemiological studies suggesting increased risks of brain tumors, acoustic neuroma and T-cell lymphoma for the mobile phone users [17–21].

In this review, we focus on papers showing complex dependence of the NT MM effects on various parameters, both physical and biological.

Experimental studies

Examples of diverse in vitro biological effects of NT MWs in the frequency range as used in mobile communication and at intensities below ICNIRP restrictions are given in Table 1. It should be noted that both negative and positive effects were observed regarding the same endpoints including genotoxic effects. However, the NT MW effects depend on several physical and biological variables. Therefore, comparison of the results from different studies should be taken with care and the original results should be compared with the data from replication studies obtained under identical conditions of exposure.

The first data on NT effects of MWs in so-called millimeter range (wavelength 1–10 mm in vacuum) was obtained by Vilenskaya and co-authors [22] Devyatkov [23], and Gründler with colleagues [24]. At lower frequency ranges, first

Table 1
Examples of diverse in vitro biological effects of NT MWs in the frequency range as used in mobile communication

Objects	Effects	Reference
Preloaded synaptosomes	Changes in calcium efflux	[29]
Reuber H35 hepatoma cells	Ornithine decarboxylase (ODC)	[67]
Rat brain cells	DNA breaks as measured with comet assay	[113]
AMA human epithelial cells	Cell proliferation	[114]
Human lymphocytes	53BP1/γ-H2AX DNA repair foci	[39]
Human lymphocytes	Changes in chromatin conformation similar to stress	[45]
Rat atrocities and porcine brain capillary endothelial cells	Permeability of an in vitro model of the BBB	[115]
Human mast cell line, HMC-1	Expression of the proto-oncogene c-kit, the transcription factor nucleoside diphosphate kinase B and the apoptosis-associated gene DAD-1	[116]
Human endothelial cell line	Activation of the hsp27/p38 MAPK stress pathway	[117]
Human peripheral blood cultures	Micronucleus frequency	[69]
Embryonic stem (ES) cells	Gene expression	[96]
Human diploid fibroblasts	DNA single- and double-strand breaks	[63]
Peritoneal neutrophils of mice	Respiratory burst induced by calcium ionophore A23187 and phorbol ester 12-myristate 13-acetate	[70]
L929 fibroblasts	Ornithine decarboxylase	[73]
Yeast cells	Cell proliferation	[9]
Yeast cells	Cell synchronization	[92]

investigations of the MW NT effects were performed by Blackman and colleagues [25–27] and Adey with colleagues [28, 29]. Since that time, other groups have confirmed the main conclusions of these studies, as will be reviewed below.

AVTD Technique

Significant body of results in our research group was obtained with the method of anomalous viscosity time dependence (AVTD). The AVTD method is a sensitive technique to detect changes in conformation of nucleoids induced by both genotoxic and stress factors.

This technique is based on the radial migration of high molecular weight DNA protein complexes such as nucleoids (nuclear matrix structure with attached DNA domains) in rotary viscometer [30–32]. The physical model of AVTD was developed by Kriuchkov et al. [33] based on the theory of radial migration [30, 34, 35]. The changes in AVTD were observed in *E. coli* cells of several strains, rat thymocytes, and human lymphocytes after exposure to MWs in vitro [36–46]. The AVTD changes have been also observed upon treatment of cells with the DNA specific chemicals such as ethidium bromide (EtBr) and etoposide VP-16 [47–49] and in response to stress induced by heat shock [39, 44, 45]. Several experimental observations have suggested that an increase in AVTD in response to MWs is caused by relaxation of DNA domains and, consequently, decrease in AVTD is caused by chromatin condensation. Single cell gel electrophoresis (comet assay) and halo assay confirmed this suggestion [50, 51].

Frequency and Power Windows

Effects of NT MWs on repair of radiation-induced DNA breaks were studied by the AVTD method in *E. coli* K12 AB1157 [38]. Significant inhibition of repair was found when X-irradiated cells were exposed to MWs within the frequency ranges of 51.62–51.84 GHz and 41.25–41.50 GHz. In both ranges, the effect was observed within specific "frequency windows" having a pronounced resonance character with the resonance frequencies of 51.76 GHz and 41.32 GHz, respectively [37, 38]. The MW effect could not be explained by heating.

Decrease in PD resulted in significant narrowing of the resonance response of *E. coli* cells to the MW exposure [37, 48]. With decreasing PD from $3 \cdot 10^{-3}$ to 10^{-19} W/cm^2, the resonance frequency of 51.755 GHz was stable within the error of measurements, ± 1 MHz. At the same time, the half-width of the resonance decreased from 100 MHz to 3 MHz. Sharp narrowing of the 51.755 GHz resonance in the PD range from $3 \cdot 10^{-3}$ to 10^{-7} W/cm^2 was followed by an emergence of new resonances: 51.675 ± 0.001, 51.805 ± 0.002, and 51.835 ± 0.005 GHz [48, 52]. The half-widths of all these resonances including the main one, 51.755 ± 0.001 GHz, were about 10 MHz at the power density of 10^{-10} W/cm^2. These data were interpreted as a splitting of the main resonance 51.755 GHz in the MW field [48]. The MW effects were studied at different PDs and several frequencies around the resonance frequency of 51.675 GHz. This resonance frequency was shown to be stable, ± 1 MHz, within the PD range of 10^{-18}–10^{-8} W/cm^2. Along with disappearance of the 51.675 GHz resonance response at higher PD of 10^{-6}–10^{-3} W/cm^2, a new resonance effect arose at 51.688 ± 0.002 GHz [52]. This resonance frequency also was stable within the PD range studied. Taken together,

these data strongly suggested a sharp rearrangement of frequency spectra of MW action, which was induced by MWs of the sub-thermal PD range. The half-widths of all three resonances studied depended on PD, changing from 2–3 MHz to 16–17 MHz (51.675 GHz and 51.668 GHz resonances) or from 2–3 MHz to 100 MHz (51.755 GHz resonance) [48, 52]. These data indicated that different dependencies of half-width on PD might be expected at various resonance frequencies.

Significant narrowing in resonance response was found when studying the growth rate in yeast cells [53] and chromatin conformation in thymocytes of rats [40]. In the Gründler's study, the half-width decreased from 16 MHz to 4 MHz as PD was decreased from 10^{-2} to 10^{-12} W/cm^2. Based on these studies with different cell types, one may suggest that narrowing of the resonance upon decrease in PD is one of the regularities in cell response to NT MWs.

Based on extrapolation from the data obtained in the extremely high frequency range (30–300 GHz), the values for half-width of resonances at the frequency range of mobile communication (0.9–2 GHz) were estimated to be 1–10 MHz [45]. Effects of Global System for Mobile Communication (GSM) MWs on chromatin conformation and 53BP1 (tumor suppressor p53 binding protein 1)/γ-H2AX (phosphorylated H2AX histone) DNA repair foci in human lymphocytes were studied in this frequency range with the increment of 5 MHz. Dependence of these MW effects on carrier frequency was observed [44, 45]. This dependence recently was replicated in independent set of experiments with lymphocytes from 20 persons in total [44, 54].

Tkalec and colleagues [55] exposed duckweed (*Lemna minor L.*) to MWs at the frequencies of 400, 900, and 1900 MHz. The growth of plants exposed for 2 h to the 23 V/m electric field of 900 MHz significantly decreased in comparison with the control, while an electric field of the same strength but at 400 MHz did not have such effect. A modulated field at 900 MHz strongly inhibited the growth, while at 400 MHz modulation did not influence the growth significantly. At both frequencies a longer exposure mostly decreased the growth and the highest electric field (390 V/m) strongly inhibited the growth. Exposure of plants to lower field strength (10 V/m) for 14 h caused significant decrease at 400 and 1,900 MHz, while 900 MHz did not influence the growth. Peroxidase activity in exposed plants varied, depending on the exposure characteristics. Observed changes were mostly small, except in plants exposed for 2 h to 41 V/m at 900 MHz where a significant increase (41%) was found. Authors concluded that MWs might influence plant growth and, to some extent, peroxidase activity. However, the effects of MWs strongly depended on the characteristics of the field exposure such as frequency and modulation.

It was found that the NT MW effects are observed within specific "PD windows" [23]. This type of PD dependence for the MW effects was observed in several studies as reviewed previously [6, 9, 10, 12, 56–58].

The data obtained in experiments with *E. coli* cells and rat thymocytes provided new evidence for this type of PD dependence [40, 42, 48, 52]. Window-like PD dependences of the MW effects were observed at different resonance frequencies. The most striking PD window was found at the resonance frequency of 51.755 GHz [48]. When exposing the *E. coli* cells at the cell density of $4 \cdot 10^8$ cell/ml, the effect reached saturation at the PD of 10^{-18}–10^{-17} W/cm^2 and did not change up to PD of 10^{-3} W/cm^2. In these experiments, the direct measurements of PD below 10^{-7} W/cm^2 were not available and lower PDs were obtained using calibrated attenuators. Therefore, some uncertainty in the evaluation of the lowest PDs was

possible. The background MW radiation in this frequency range has been estimated as 10^{-21}–10^{-19} W/m^2/Hz [59]. Based on the experimentally determined half-width of resonance of 1 MHz [48], the background PD was estimated as 10^{-19}–10^{-17} W/cm^2 within the 51.755 GHz resonance. The resonance MW effects were observed at PD very close to the estimated background value in experiments with *E. coli* cells [43, 48, 52, 60, 61]. The data suggested that the PD dependence of MW effect at specific resonance frequencies might have a threshold comparable with the background level.

Dependence of the MW effect on PD at one of resonances, 51.675 GHz, had the shape of "window" in the PD range from 10^{-18} to 10^{-8} W/cm^2 [52]. It is interesting, that no MW effect was observed at subthermal and thermal PDs. This type of PD dependence clearly indicated nonthermal mechanism of the MW effects observed. The position of the PD window varied between different resonance frequencies and depended on cell density during exposure of cells.

Despite some uncertainty in the evaluation of PD at the levels below 10^{-7} W/cm^2 in the referred studies the data indicated that MWs at specific resonance frequencies result in biological effects at very low intensities comparable with intensities from base stations and other MW sources used in mobile communication.

Duration of Exposure and Time After Exposure

Bozhanova with coauthors [61] reported that the effect of cellular synchronization induced by NT MWs depended on duration of exposure and PD. The dependence on duration of exposure fitted to exponential function. An important observation was that the decrease in PD could be compensated by the increase in the duration of exposure in order to achieve the same synchronization of cells.

MW exposure of *E. coli* cells and rat thymocytes at PDs of 10^{-5}–10^{-3} W/cm^2 resulted in significant changes in chromatin conformation if exposure was performed at resonance frequencies during 5–10 min [38, 40, 41]. Decreasing of PD by orders of magnitude down to 10^{-14}–10^{-17} W/cm^2 could be compensated by several-fold increasing of exposure time to 20–40 min in order to achieve the same changes in conformation of nucleoids [60]. The duration of exposure should be longer, more than 1 h, to achieve the same effect at the lowest estimated PD of 10^{-19} W/cm^2 [60]. The effects were more sensitive to duration of exposure than to PD in the range of 10^{-17}–10^{-6} W/cm^2 [60]. Therefore, decreasing of PD by orders of magnitude could be compensated by several-fold increasing of exposure time and duration of exposure to NT MWs may have a significantly larger role than PD.

The MW effects depended on postexposure time. This dependence of the MW effect on *E. coli* cells had an initial phase of increase about 100 min followed by the phase, which was close to a plateau, around 100 min [43, 60, 62]. A trend to decrease in effect was observed at longer times up to 300 min [43, 62]. Significant MW-induced changes in chromatin conformation were observed when rat thymocytes were lysed in between 30–60 min after exposure to MWS [40]. This effect nearly disappeared if the cells were incubated more than 80 min between exposure and analysis.

In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to MWs from the GSM mobile phones [39, 44]. MWs induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. It was found in the same

and following studies that GSM MWs at the carrier frequency of 915 MHz and UMTS (Universal Mobile Telecommunications System) MWs at the 1947.4 MHz (middle channel) inhibited formation of the 53BP1/γ-H2AX DNA repair foci and these adverse effects remained during 72 h after 1 h exposure [40, 44, 54].

The data suggested that there is a time window for observation of the MW effects, which may be dependent on endpoint, cell type, duration and, PD of exposure.

Intermittence and Coherence Time of Exposure

Diem and colleagues [63] exposed cultured human diploid fibroblasts and cultured rat granulosa cells to intermittent and continuous MWs (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; during 4, 16 and 24 h; intermittent 5 min on/10 min off or continuous wave). Comet assay was applied to analyze DNA single- and double-strand breaks. MW-induced effects occurred after 16 h exposure in both cell types and after different mobile-phone modulations. The intermittent exposure showed a stronger effect than continuous exposure.

An interesting study with MW exposure of L929 fibroblasts was performed by the group of Litovitz [64]. MWs at 915 MHz modulated at 55, 60, or 65 Hz approximately doubled ornithine decarboxylase (ODC) activity after 8 h. Switching modulation frequencies from 55 to 65 Hz at coherence times of 1.0 s or less abolished enhancement, while times of 10 s or longer provided full enhancement. These results suggested that the microwave coherence effects are remarkably similar to those observed previously with extremely low frequency (ELF) magnetic fields by the same authors.

Polarization

The effects of circularly polarized (CP) MWs were studied in *E. coli* cells at the frequencies from two frequency windows (resonances) that were identified using linearly polarized (LP) MWs, 51.62–51.84 GHz and 41.25–41.50 GHz. At the resonance frequency of 51.76 GHz, right-handed CP MWs inhibited repair of x-ray-induced DNA damages [37, 41]. In contrast to right-handed polarization, left-handed CP MWs had virtually no effect on the DNA repair, while the efficiency of LP MWs was in-between of 2 circular polarizations. Inversion in effectiveness of circular polarizations was observed at the resonance frequency of 41.32 GHz. In contrast to the frequency of 51.76 GHz, left-handed CP MWs at 41.32 GHz significantly inhibited DNA repair, while right polarization was almost ineffective. MWs of the same CP affected cells at several tested frequencies within each resonance, other CP being always ineffective [37, 41, 42]. Therefore, a sign of effective CP, left or right, was the attribute of a whole resonance. Two different types of installation, based either on spiral waveguides [41] or quarter-wave mica plates [37, 42, 46, 52, 65] were used to study the dependences of the MW effects on polarization. Similar results were observed regardless the way of producing the MWs of different polarizations.

Pre-irradiation of *E. coli* cells to x-rays inverted the sign of effective polarization [37, 42]. This inversion was observed for 2 different resonances, 41.32 and 51.76 GHz. Neither resonance frequencies, nor half-widths of the resonance changed during the inversions in effective CPs. The effects of left- and right-handed CP MWs become the same at 50 cGy [37]. At this dose, about one single-stranded

DNA break per haploid genome was induced and this dose was too low to damage significantly any cellular structure except for DNA. It is known that a nucleoid in *E. coli* cells consists of the supercoiled DNA-domains. It is believed that the majority of DNA in living cells has a right-handed helicity (B-form) but a minor part, in order of one percent, may be in the form of a left-handed helix (Z-form). X-ray-induced DNA breaks result in relaxation of DNA-domains. On the other hand, supercoiling is connected with transitions between right B-form to left Z-form in some DNA sequences. Therefore, the data suggested that difference in biological effects of polarized MWs might be connected with DNA helicity and supercoiling of DNA-domains.

Supercoiling of DNA-domains is changed during cell cycle because of transcription, replication, repair, and recombination. It also can be changed by means of DNA-specific intercalators such as ethidium bromide (EtBr). EtBr changes supercoiling and facilitates the transition of DNA sequences from Z-form to B-form. Preincubation of *E. coli* AB1157 cells with EtBr, 1 μg/ml, inverted the effective polarization at the resonance frequency of 51.755 GHz and right-handed MWs became more effective than left polarization [46]. EtBr changed the supercoiling of DNA domains starting at a concentration of 1 μg/ml as measured with the AVTD in different cell types including *E. coli* [47, 48, 51]. The data provided further evidence that DNA may be a target for the NT MW effects.

Investigations of NT MW effects at 15 resonances in *E. coli* cells and 2 resonances in Wistar rat thymocytes provided evidence that one of two circular polarizations is always more effective than another one [36, 37, 40–43, 46, 52, 65, 66]. These data are summarized in Table 2. In all experiments, the effect of linear polarized MWs was in between the effects of 2 circular polarizations. Obviously, the difference in effects of right and left polarizations could not be explained by heating or by mechanism dealing with "hot-spots" due to unequal SAR distribution. The data about the difference in effects of differently polarized MWs, inversion of effective circular polarization between resonances and after irradiation of cells with x-rays and incubation with EtBr provided clear evidence for nonthermal mechanisms of MW effects. These data could be interpreted as evidence for either an asymmetrical nature of the target for the NT MW effects, which is presumably chromosomal DNA [37], or existence of selection rules on helicity if quantum-mechanical approach is applied [42].

Modulation

There is experimental evidence for the role of modulation in the NT MW effects both in vitro and in vivo [29, 67–77].

Examples for dependence of MW effects on modulation include different types of modulation including amplitude, speech, and phase modulations. Amplitude modulation 16 Hz but not 60 Hz or 100 Hz modulated MWs, 450 MHz, increased activity of ODC [67]. Speech-modulated 835 MHz MWs produced no effect on ODC as compared to typical signal from a TDMA (Time Division Multiple Access) digital cellular phone [75]. Phase-modulated GSM-1800 MWs (Gaussian Minimum Shift Keying, GMSK) at 1.748 GHz, induced micronuclei in human lymphocytes while CW MWs did not [69].

Gapeev and coauthors [70] studied effects of MW exposure on the respiratory burst induced by calcium ionophore A23187 and phorbol ester 12-myristate 13-acetate (PMA) in the peritoneal neutrophils of mice. MWs at the PD of 50 $\mu W/cm^2$

Table 2
Summary of polarization studies*

Cells	Resonance frequency, GHz	Effective circular polarization
E. coli K12 N99(λ, $\lambda imm^{434} bio^{10}$)	41.277 ± 0.002	Right-handed
Wistar rat thymocytes	41.303 ± 0.001	Right-handed
E. coli K12 N99(λ)	41.305 ± 0.001	Right-handed
E. coli K12 AB1157	41.32 ± 0.01	Right-handed
E. coli K12 N99	41.324 ± 0.001	Right-handed
Wistar rat thymocytes	41.61 ± 0.01	Left-handed
E. coli K12 AB1157	51.425 ± 0.001	Left-handed
E. coli K12 AB1157	51.575 ± 0.001	Right-handed
E. coli K12 AB1157	51.675 ± 0.001	Left-handed
E. coli K12 N99(λ, $\lambda imm^{434} bio^{10}$)	51.723 ± 0.001	Left-handed
E. coli K12 N99(λ)	51.740 ± 0.001	Left-handed
E. coli K12 AB1157	51.755 ± 0.001	Left-handed
E. coli K12 N99	51.765 ± 0.002	Left-handed
E. coli K12 AB1157	51.805 ± 0.002	Right-handed
E. coli K12 AB1157	51.835 ± 0.005	Left-handed
E. coli K12 AB1157	51.857 ± 0.001	Left-handed
E. coli K12 AB1157	51.955 ± 0.001	Right-handed

*NT MWs affected nucleoids in *E. coli* cells and Wistar rat thymocytes within specific frequency windows (resonances). Each resonance was characterized by a specific CP (right- or left-handed) that was effective, while another CP was not, other conditions of exposure being the same.

inhibited the respiratory burst. MW effect depended on frequency and was maximal at the frequency of 41.95 GHz. Opposite effect, stimulation of the respiratory burst, was observed upon modulation of MWs with the frequency of 1 Hz. Only this modulation out of four tested (0.1, 1, 16, and 50 Hz) resulted in stimulation of the respiratory burst.

Huber with coauthors [71] investigated effects of MWs similar to those used in mobile communication, a "base-station-like" and a "handset-like" signal (10 g tissue-averaged spatial peak-specific absorption rate of 1 W/kg for both conditions), on waking regional cerebral blood flow (rCBF) in 12 healthy young men. The effect depended on the spectral power in the amplitude modulation of the carrier frequency such that only "handset-like" MW exposure with its stronger low-frequency components but not the "base-station-like" MW exposure affected rCBF. This finding supported previous observations of these authors that pulse modulation of MWs is necessary to induce changes in the waking and sleep EEG, and substantiated the notion that pulse modulation is crucial for MW-induced alterations in brain physiology.

Markkanen and colleagues [74] exposed cdc48-mutated *Saccharomyces cerevisiae* yeast cells to 900 or 872 MHz MWs with or without exposure to ultraviolet (UV) radiation and analyzed apoptosis. Amplitude modulated

(217 pulses per second) MWs significantly enhanced UV induced apoptosis in cells, but no effect was observed in cells exposed to unmodulated fields at the identical time-average SAR of 0.4 W/kg that was lower the ICNIRP safety standards.

Persson with colleagues [76] studied effects of MWs of 915 MHz as CW and pulse-modulated with different pulse power and at various time intervals on permeability of the BBB in Fischer 344 rats. Albumin and fibrinogen were demonstrated immunochemically and classified as normal versus pathological leakage. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. The frequency of pathological rats significantly increased in all exposed rats. Grouping the exposed animals according to the level or specific absorption energy (J/kg) gave significant difference in all levels above 1.5 J/kg. The exposure was 915 MHz MWs either pulse modulated at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width, or CW. The frequency of pathological rats was significantly higher in MW-exposed groups than in controls and the frequency of pathological rats after exposure to pulsed radiation was significantly less than after exposure to CW.

Significant amount of in vivo studies under varying parameters of exposure (intensity, frequency, exposure time, modulation, intermittence) have been performed in Russia/Soviet Union and published in Russian. Retrospective analysis of 52 Russian/Soviet in vivo studies with animals (mice, rats, rabbits, guinea pigs) on chronic exposure to MWs has been recently published in Russian [7]. In these studies, various endpoints were measured up to 4 months of chronic exposure including analysis of: weight of animal body, histological analysis and weight of tissues, central nervous system, arterial pressure, blood and hormonal status, immune system, metabolism and enzymatic activity, reproductive system, and teratogenic and genetic effects. Based on their analysis, the authors concluded that exposure to modulated MWs resulted in bioeffects, which can be different from the bioeffects induced by CW MWs; acute exposure to modulated MWs at low intensities (nonthermal levels) could result in development of unfavorable effects; direction and amplitude of the biological response to non-thermal MW, both in vitro and in vivo, depended on type of modulation; often, but not always, modulated MWs resulted in more pronounced bioeffects than CW MW; the role of modulation was more pronounced at lower intensity levels.

One review of the Russian/Soviet studies is available in English [14]. These authors conclude that "a number of good-quality studies have convincingly demonstrated significant bioeffects of pulsed MWs. Modulation often was the factor that determined the biological response to irradiation, and reactions to pulsed and CW emissions at equal time-averaged intensities in many cases were substantially different."

In conclusion, significant amount of in vitro and in vivo studies from different research groups clearly indicated dependence of the NT MW effects on modulation.

Electromagnetic Environment

Hypothetically, background EMF might be important for the MW effects. This hypothesis is based on the experimental observations that SMF, ELF magnetic fields, and MWs at low intensities induced similar effects in cells under specific conditions of exposure [3, 39, 78–80]. Despite that very little has been done for mechanistic explanation of such effects, there are attempts to consider the effects

of EMFs in a wide frequency range in the frames of the same physical models [5, 81–84].

Litovitz and colleagues [73] provided experimental evidence that the ELF magnetic noise inhibited the effects of MWs on ODC in L929 cells. The ODC enhancement was found to decrease exponentially as a function of the noise root mean square amplitude. With 60 Hz amplitude-modulated MWs, complete inhibition was obtained with noise levels at or above 2 μT. With the DAMPS (Digital Advanced Mobile Phone System) cellular phone MWs, complete inhibition occurred with noise levels at or above 5 μT. Further studies by the same group revealed that the superposition of ELF noise inhibited hypoxia de-protection caused by long term repeated exposures of chick embryos to MWs [85].

Usually, all electric devices were shut down during Gründler's experiments with yeast cells in order to decrease the electromagnetic noise (personal communication). SMF was controlled in Gründler's experiments and in attempts to replicate these experiments by Gos and colleagues [86].

Ushakov with coauthors [65] exposed *E. coli* cells to MWs at the PD of 10^{-10} W/cm^2 and the frequencies of 51.675, 51.755, and 51.835 GHz. In this study, cells were exposed to MWs at various values of SMF: 22, 49, 61, or 90 μT. The authors observed dependence of the MW effects on SMF during MW exposure.

If confirmed, the observations on dependence of the NT MW effects on SMF and ELF stray field would be of significant interest for further development of physical theory for the NT MW effects and development of practical approaches to minimize the adverse effects of MWs from mobile communication.

Cell-to-Cell Interaction in Response to MWs

The effects of NT MWs at the resonance frequency of 51.755 GHz on conformation of nucleoids in *E. coli* cells were analyzed in dependence on cell density during exposure [60]. The per-cell-normalized effect of MWs increased by a factor of 4.7 ± 0.5 on average with increase in cell density by one order of magnitude, from $4 \cdot 10^7$ to $4 \bullet 10^8$ cell/ml. These data suggested a cooperative nature of cell response to MWs, which is based on cell-to-cell interaction during exposure. This suggestion was in line with the observed partial synchronization of cells after exposure to MWs.

The cooperative nature of cell response to MW at the resonance frequency of 51.755 GHz was confirmed in further studies with *E. coli* cells [48, 52, 62]. In addition, dependence of the per-cell-normalized effect on cell density was observed for two other resonances, 51.675 GHz and 51.688 GHz. These data suggested that the dependence on the cell density during exposure is a general attribute of the resonance response of *E. coli* cells to NT MWs. At the cell density of $4 \cdot 10^8$ cells/ml, the average intercellular distance was approximately 13 μm that is 10 times higher than linear dimensions of *E. coli* cells [40, 62]. Therefore, no direct physical contact seemed to be involved in the cell-to-cell interaction. Two mechanisms, biochemical and electromagnetic, were considered to account for the co-operative nature in the resonance response to weak EMF in wide frequency range including ELF, MWs and ionizing radiation [61, 87, 88]. The first one, biochemical, is based on release of secondary chemical messengers (ions, radicals, or molecules) by those cells, which were directly targeted. Via diffusion, these messengers can induce response in other cells. The second mechanism, electromagnetic, is based on reemission of secondary photons. According to this mechanism, reemitted photons can induce

response in other cells if the intercellular distance is shorter than the length of photon absorption. Our experimental data on MW effects fitted better to the electromagnetic mechanism but a combination of two mechanisms was also possible [40, 62]. In particular, radicals with prolonged lifetimes could be involved in the observed cell-to-cell communication during response to EMF [88].

The absorption length of photons with the frequencies of 10^{12}–10^{13} Hz corresponds to the intracellular distance at the cell density of $5 \cdot 10^8$ cell/ml, at which saturation in the dependences of the EMF effects on the cell density was observed [60, 62, 88, 90]. Such photons may be involved in cell-to-cell communication according to the electromagnetic mechanism and in agreement with the prediction of Fröhlich that biosystems support coherent excitations within frequency range of 10^9–10^{12} Hz [91]. From this point of view, cell suspension may respond to NT MWs as a whole. In this case, the number of the exposed cells should be large enough to facilitate cell-to-cell communication during the responses to MWs at specific parameters of exposure such as frequency, modulation, and polarization. Interestingly, the cell density for saturation of both MW and ELF effects was about $5 \cdot 10^8$ cell/ml that is close to cell densities in soft tissues of eukaryotes [62, 91]. Such density of cells in the tissues may be important for regulation of living systems by electromagnetic cell-to-cell communication. Cellular membranes and DNA have been considered as possible sources of coherent excitations and photons, which may be involved in electromagnetic cell-to-cell communication [49, 88, 91].

PD dependences of the MW effect at the 51.755 GHz resonance frequency were considerably different between two cell densities, $4 \cdot 10^7$ cells/ml and $4 \cdot 10^8$ cells/ml [49]. However, the resonance frequency of 51.755 GHz did not shift with the changes in cell density. The half-width of the 51.755 GHz resonance did not depend on cell density either. Contrary to the 51.755 GHz resonance response, the half-width of the 51.675 GHz resonance depended on cell density [53]. The data suggested that intracellular interaction during the NT MW exposures at some specific frequencies might affect subcellular targets for NT MWs. This target is presumably chromosomal DNA that is organized in the DNA domains [36, 37, 84].

In all studies concerning dependence of the MW effects on cell density, the cells occupied a negligible part of the exposed volume and could not change the absorption of MWs even at the highest cell densities [48, 53, 60, 61]. Striking difference in the cell responses at various cell densities provided further evidence for non-thermal mechanism of the observed MW effects.

Significant MW effect on synchronization of *Saccharomyces carlsbergensis* yeast cells were observed by Golant and coauthors [92]. Exposure to MWs at 30 μW/cm^2 and 46 GHz induced synchronization as measured by cell density and bud formation. This synchronization lasted more than 20 cell cycles after exposure. Authors assumed that MWs induced cell-to-cell interaction resulting in the observed synchronization.

Genetic, Gender-Related and Individual Differences

We studied effects of MWs on *E. coli* cells of three isogenic strains with different length of chromosomal DNA [36]. Bacterial chromosomal DNA in N99 wild type cells was lengthened by inserting DNA from λ and $\lambda imm^{434} bio^{10}$ phages. Lysogenic strains N99(λ) and N99(λ, $\lambda imm^{434} bio^{10}$) obtained were used for MW exposure along with the wild type N99 strain. The response of each strain was studied at

10–17 frequencies inside 41.24–41.37 GHz and 51.69–51.795 GHz frequency ranges at 10^{-10} W/cm^2. Clear resonance responses were observed for each strain in both frequency ranges [36]. Significant shifts of both resonance frequencies were found between strains (Table 3). The shifted resonances had the same amplitude and half-width as for N99 cells [36]. Upon shifting, no changes in effective circular polarization within each shifted resonance were observed (Table 3). The shifts in resonance frequencies could not be explained by activity of additional genes inserted with the phage DNA. For example, *cI* and *rex* genes are active in lysogenic N99 (λ) strain. Nevertheless, the $\lambda\, imm^{434} bio^{10}$ insertion did not contain immunity region and therefore, the *cI* and *rex* genes. Moreover, this genome is identical to the genome of phage λ but about 23% shorter because of the bio^{10} deletion. Therefore, it was unlikely that shifts of resonances were caused by additional gene activity upon insertion of $\lambda\, imm^{434} bio^{10}$. On the other hand, the theoretical consideration based on oscillations of the DNA-domains regarding a whole nucleoid provided good correlation between the increasing in the DNA length and the shifts in resonances [36].

A detailed analysis of MW effects on *E. coli* AB1157 cells at 10^{-10} W/cm^2 and various frequencies revealed the resonance frequency of 51.755 ± 0.001 GHz [48]. This value was statistically significantly different from the resonant frequency of 51.765 ± 0.002 in response of *E. coli* N99 cells to MWs in the same frequency range [48]. It should be noted that both strains, AB1157 and N99, are considered as wild type strains. Nevertheless, these strains are different in their genotypes by several specific gene markers [38, 93]. These data suggested that strains of different origin, even being considered as wild type strains, might have different resonance responses to NT MWs.

Stagg with colleagues [94] exposed tissue cultures of transformed and normal rat glial cells to packet-modulated MWs (TDMA that conforms to the North American digital cellular telephone standard) at 836.55 MHz. Results from the DNA

Table 3

Genomic differences influenced response of cells to MWs. Experimentally determined resonance frequencies, effective CP, and shifts between resonances for three *E. coli* strains, N99, N99(λ), and N99(λ, $\lambda\, i^{434}\ bio^{10}$), which were isogenic but different in the length of genome.

Frequency band	*E. coli* strain and genome length, Mb:	N99 4.20	N99(λ) 4.249	N99(λ, $\lambda\, i^{434}\ bio^{10}$) 4.286
41.240–41.370 GHz	Resonance frequency, GHz	41.324 ± 0.001	41.305 ± 0.001	41.277 ± 0.002
	Effective circular polarization	Right-handed	Right-handed	Right-handed
	Shift in respect to N99, MHz	0	19 ± 2	47 ± 4
51.690–51.795 GHz	Resonance frequency, GHz	51.765 ± 0.002	51.740 ± 0.001	51.723 ± 0.001
	Effective circular polarization	Left-handed	Left-handed	Left-handed
	Shift in respect to N99, MHz	0	25 ± 3	42 ± 3

synthesis assays differed for these 2 cell types. Sham-exposed and MW-exposed cultures of primary rat glial cells showed no significant differences for either log-phase or serum-starved condition. C6 glioma cells exposed to MWs at 5.9 μW/g SAR (0.9 mW/cm^2) exhibited small (20–40%) but significant increases in 38% of [^{3}H]-thymidine incorporation experiments.

Repacholi with coauthors [95] chronically exposed wild-type mice and E mu-Pim1 transgenic mice, which are moderately predisposed to develop lymphoma spontaneously, to plane-wave pulse-modulated MWs at 900 MHz with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms. Incident power densities were 2.6–13 W/m^2 and SARs were 0.008–4.2 W/kg, averaging 0.13–1.4 W/kg. The lymphoma risk was found to be significantly higher in the exposed transgenic mice. No effects were seen in the wild type mice.

Czyz with colleagues [96] exposed pluripotent embryonic stem (ES) cells of wild-type and deficient for the tumor suppressor p53 to pulse modulated GSM MWs at 1.71 GHz. Two dominant GSM modulation schemes (GSM-217 and GSM-Talk), which generate temporal changes between GSM-Basic (active during talking phases) and GSM-DTX (discontinuous transmission, which is active during listening phases thus simulating a typical conversation), were applied to the cells at and below the ICNIRP safety standards. GSM-217 MWs induced a significant upregulation of mRNA levels of the heat shock protein, hsp70 of p53-deficient ES cells differentiating in vitro, paralleled by a low and transient increase of c-jun, c-myc, and p21 levels in p53-deficient, but not in wild-type cells. Theses data indicated that the genetic background determines cellular responses to GSM MWs. No responses were observed after MW exposure to GSM-Talk applied at similar slot-averaged SAR, but at lower time-averaged SAR values.

There are studies indicating that MWs may exert a gender-related influence on brain activity [97–99]. Papageorgiou with coauthors investigated the gender-related influence of MWs, similar to that emitted by GSM900 mobile phones, on brain activity [?]. Baseline electroencephalographic (EEG) energy of males was greater than that of females, while exposure to MWs decreased EEG energy of males and increased that of females. Memory performance was invariant to MW exposure and gender influences. Smythe and Costall reported the effects of mobile phone exposure on short- and long-term memory in male and female subjects [99]. The results showed that males exposed to an active phone made fewer spatial errors than those exposed to an active phone condition, while females were largely unaffected. These results further indicated that mobile phone exposure has functional consequences for human subjects, and these effects appear to be sex-dependent.

We analyzed effects of GSM MWs on chromatin conformation in human lymphocytes from peripheral blood [45]. The MW effects varied between individuals. Exposure of 30 min to MWs at 900 and 905 MHz resulted in statistically significant condensation of chromatin in lymphocytes from one out 3 tested donors. This condensation was similar to effects of heat shock within the temperature window of 40–44°C. Stronger effects of MWs were found following one-hour exposure. In replicated experiments, cells from 4 out 5 donors responded to 905 MHz. Statistically significant response to 915 MHz was observed in cells from one out five donors. Dependent on donor, condensation, 3 donors, or decondensation, one donor, of chromatin was found in response to one-hour exposure. Effects of MWs correlated statistically significantly with effects of heat shock and initial state of chromatin before exposure.

Significant individual variations in effects of GSM and UMTS MWs on chromatin conformation and 53BP1/γ-H2AX DNA repair foci in human lymphocytes were observed in further studies [39, 44, 54]. Despite some trends to different response between lymphocytes from hypersensitive to EMF subjects and matched healthy controls [39], these differences were not statistically significant between groups. These studies provided unequivocal evidence that GSM and UMTS MWs induce adverse effects in lymphocytes from hyperelectrosensitive subjects. The reasons, why significant variations in response of cells were observed in both hyperelectrosensitive and control groups of subjects, remain to be investigated.

Zotti-Martelli with colleagues [100] exposed peripheral blood lymphocytes from 9 different healthy donors for 60, 120, and 180 min to CW MWs with a frequency of 1800 MHz and PDs of 5, 10, and 20 mW/cm^2 and analyzed DNA damage using micronucleus (MN) assay. Both spontaneous and induced MN frequencies varied in a highly significant way among donors, and a statistically significant increase of MN, although rather low, was observed dependent on exposure time and PD. Authors concluded that MWs are able to induce MN in short-time exposures to medium PD fields. The data analysis highlighted a wide inter-individual variability in the response, which was replicated in further experiments.

Physiological Variables

The importance of physiological variables, which may include all conditions of cell culture growth such as aeration, the composition of the growth and exposure media has been reviewed previously by Gründler and colleagues [9].

Lai and Singh [101] described effects of MWs on the rat brain cells as measured using a microgel electrophoresis assay. These effects were significantly blocked by treatment of rats either with the spin-trap compound N-tert-butyl-α-phenylnitrone or with melatonin that is potent free radical scavenger and antioxidant [99]. These data suggested that radicals might be involved in the effects of MWs and provided further evidence for dependence these effects on physiological variables. Other groups confirmed this suggestion in further studies.

Oktem with colleagues [102] exposed rats to MWs from GSM900 mobile phone with and without melatonin treatment. Malondialdehyde (MDA), an index of lipid peroxidation, and urine N-acetyl-beta-d-glucosaminidase (NAG), a marker of renal tubular damage, were used as markers of oxidative stress-induced renal impairment. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate the changes of antioxidant status. In the MW-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment inhibited these effects. The authors concluded that melatonin might exhibit a protective effect on mobile phone-induced renal impairment in rats.

Ozguner with colleagues [103] exposed Wistar-Albino rats to MWs from GSM900 mobile phone with and without melatonin and analyzed histopathologic changes in skin. MW induced increase in thickness of stratum corneum, atrophy of epidermis, papillamatosis, basal cell proliferation, granular cell layer (hypergranulosis) in epidermis and capillary proliferation. Impairment in collagen tissue distribution and separation of collagen bundles in dermis were all observed in exposed animals as compared to the control group. Most of these changes, except

hypergranulosis, were prevented with melatonin treatment. The authors concluded that exposure to GSM900 MWs emitted by mobile phones caused mild skin changes and melatonin treatment could reduce these changes.

Ilhan with coauthors [104] investigated oxidative damage in brain tissue of rats exposed to GSM900 MWs with and without pretreatment with Ginkgo biloba (Gb). MWs induced oxidative damage measured as: (i) increase in MDA and nitric oxide (NO) levels in brain tissue; (ii) decrease in brain SOD and GSH-Px activities; and (iii) increase in brain xanthine oxidase and adenosine deaminase activities. These MW effects were prevented by Gb treatment. Furthermore, Gb prevented the MW-induced cellular injury in brain tissue revealed histopathologically. Authors concluded that reactive oxygen species may play a role in adverse effects of GSM900 MWs and Gb prevents the MW-induced oxidative stress by affecting antioxidant enzymes activity in brain tissue.

In our investigations, *E. coli* cells were exposed to CP or LP MWs ($100\,\mu W/cm^2$) at the resonance frequencies of 41.32 GHz and 51.76 GHz [36, 60]. Both value and direction of the MW effects strongly depended on the phase of culture growth. At logarithmic phase of growth, MWs resulted in condensation of nucleoids. In contrast, MW exposure decondensed nucleoids in cells if exposure was performed at the stationary phase of growth. It is known, that the state of nucleoid condensation depends on cell activity. In stationary cells nucleoids are more condensed compared to logarithmic cells that divide actively. We concluded that MWs are able either stimulate or inhibit activity of the cells in dependence on stage of growth, stationary or logarithmic, respectively. Higher variability in effects was observed for logarithmic phase and effects were more stable for the stationary phase that is characterized by partial synchronization of cells [36, 60]. There was no effect at all if cells were exposed at the end of the logarithmic phase where the MW effects changed their direction from inhibition to stimulation [60]. Another peculiarity was observed at the very beginning of the logarithmic stage, where the condensation of chromatin induced by MWs was very weak. The AVTD data were confirmed by the electrophoretic analysis of proteins bound to DNA [36]. The main feature of the effect in the stationary phase was a decrease in the quantity of several unidentified DNA-bound proteins with molecular weights of 61, 59, 56, 26, and 15 kDa. In contrast, the main trend was an increase in some proteins, 61, 56, 51, and 43 kDa after exposure at the logarithmic phase. The decrease or increase in the level of proteins bound to DNA correlated with the observed changes in the state of nucleoids, decondensation or condensation, respectively.

The MW effects was studied both at stationary and logarithmic phase of growth during exposure to MWs in the PD range of 10^{-18} to $3 \cdot 10^{-3}\,W/cm^2$ at various cell densities [62]. Relatively weak response to MWs was observed in exponentially growing cells. Partially synchronized stationary cells were more sensitive, especially at the cell densities above 10^8 cell/ml. The data suggested that the cooperative response of cells to MWs might vary in dependence on phase of growth.

Recent data by Ushakov and colleagues [65] indicated that the MW effects on *E. coli* cells depended on concentration of oxygen in the cell suspension during exposure. This dependence might suggest that oxygen concentration should be indicated in order to improve reproducibility.

Summary of Experimental Studies

Numerous experimental data have provided strong evidence for NT MW effects and have also indicated several regularities in these effects:

dependence of frequency within specific frequency windows of "resonance type";
dependence on modulation and polarization; dependence on intensity within specific intensity windows including superlow PDs comparable with intensities from base stations/masts;
narrowing of the frequency windows with decrease in intensity;
higher sensitivity of the NT MW effects to duration of exposure than to PD in the range of 10^{-17}–10^{-6} W/cm^2, therefore, duration of exposure may have significantly larger role as compared to PD;
dependence on cell density that suggests cell-to-cell interaction during response to NT MWs;
a potential of radical scavengers/antioxidants to abolish the MW effects;
dependence on physiological conditions during exposure;
genomic differences can influence response to NT MWs; and while not yet confirmed, observations that oxygen concentration, SMF, and EMF stray field during exposure may be of importance for the effects of NT MWs.

Replication Studies

An important issue to stress is that the NT MW effects depend on a number of physical parameters and biological variables. Obviously, not taking into account these dependences may result in misleading conclusions regarding the reproducibility of the NT MW effects. Especially important might be the observations that NT MWs could inhibit or stimulate the same functions [12]. Under different conditions of exposure, MWs either increased or decreased the growth rate of yeast cells [9], the radiation-induced damages in mice [105], the respiratory burst in neutrophils of mice [70], the condensation of nucleoids in *E. coli* cells [36, 60], and human lymphocytes [45]. Potentially, bidirectional effects of MWs should be taken into account in replication studies.

Despite of considerable body of studies with NT MWs in biology, only a few studies were performed to replicate the original data on the NT MW effects. It should be noted, that these "replications" usually are not comparable with the original studies because of either missing description of important parameters of exposure or significant differences in these parameters between original study and replication.

One known attempt to replicate the results of Gründler [9] was the study by Gos and coauthors [86]. No MW effects were observed in this study. However, the deviations from the Gründler's protocol might be a simple reason for poor reproducibility. For example, synchronized cells were used in studies of Gründler. Gos used, contrary to the Gründler's original protocol, exponentially growing cells. If the MW effects in yeast cells are dependent on stage of growth, cell density and intercellular interactions as it has been described for *E. coli* cells [36, 48, 52, 60], no response should be expected in the logarithmic phase of growth. Gos and colleagues used *S. cerevisiae* strain with the auxotrophy mutations for leucine and uracil. The wild type strain was used by Gründler. It might suggest another cause for the deviations between the data of Gründler and Gos. Despite orientation of

SMF in respect to electric and magnetic components of MWs was the same, the values of SMF were different. The stray ELF field was 120 nT in the study by Gos that is higher than usually observed background fields, < 50 nT. The spectral characteristics of the background fields, which were described only in the study by Gos, might be also different. In addition, the conditions of cell cultivation might vary between studies; for example, the data on oxygen concentration in the media is not available.

The amount of already known physical and biological variables that are important for reproducibility of the NT MW effects seem to be far beyond the limits of usually controlled parameters in biological experiments. The knowledge of some of these variables is based on consistent findings following from experimental studies of different research groups. Further evaluation of variables that are important for the NT MW effects would benefit from the developing of the physical and molecular biological models for the MW effects.

Most reviews of the experimental studies do not include analysis of various biological variables and physical parameters when comparing the data on NT MW effects from different studies. As result, misleading conclusion is often made that MWs at NT levels produce no "reproducible" effects. Bearing in mind the importance of several critical physical and biological variables for reproducibility of the MW effects and based on the available replication studies, we would suggest the next analogy in response to claims that there are no reproducible NT MW effects. These claims would be similar to a situation if one would use a TV-set with the wrong broadcasting system, for example PAL/SECAM in U.S. or NTSC in Europe, and based on seeing nothing would conclude that ones inability to receive favorite channels is a good evidence for the absence of stable TV broadcasting in U.S./Europe.

Possible Mechanisms

The fundamental question is how MWs at so low intensities affect living systems? Analyzing theoretically our experimental data on the MW effects at super-low intensities we concluded that these effects should be considered using quantum-mechanical approach [60]. Reanalysis of our data by Binhi [5] resulted to the same conclusion. This is in line with the fundamental mechanism that has been suggested by Fröhlich [91]. Our data also indicated that chromosomal DNA is a target for interaction with MWs [36, 37, 46].

The length of genomic DNA is much longer than the dimension of surrounding compartment. For example, there is about 1.8 m of DNA in a human genome that should be compacted in interaction with other compounds such as proteins, RNA and ions to fit into a nucleus with a characteristic diameter of 5–10 μm. Importantly, concentration of DNA in nuclei is higher than in crystallization solutions for DNA, 50–100 mM versus 10–30 mM DNA, respectively. Whether DNA is organized in nuclei as a liquid crystal remains to be investigated. However, it is clear that DNA in a living cell cannot be considered as an aqueous solution of DNA molecules in thermodynamic equilibrium.

The quantum-mechanical physical model for primary interaction of MWs with DNA has been proposed [106]. We hypothesized that genomic DNA contain two different codes [88]. The first one is well-known genetic triplet code for coding of genes. The second one is a "physical code" that determine the spectrum of

natural oscillations in chromosomal DNA including electromagnetic, mechanical, and acoustic oscillations, which are hypothetically responsible for regulation of gene expression at different stages of ontogenesis and for genomic rearrangements in evolution. The physical model describing these coupled oscillations in chromosomal DNA has been proposed [36]. This model helps to resolve so-called C-paradox that addresses the issue of a genome size, so-called C-value. In almost all eukaryotic genomes, only small percentage of DNA encodes genes. The same amount of DNA is involved in regulation of gene expression by known biochemical mechanisms. The function of the rest of DNA, which that does not depend on complexity of eukaryotic species and is represented by noncoding repetitive DNA sequences, is not understood in molecular biology providing a basement for hypotheses such as "junk DNA." The function of this major part of genomic DNA became clear given that the whole genomic DNA is considered to be responsible for the creation of the natural spectrum of oscillations that is hypothetically a main characteristic of each biological species [36].

Were the Real Signals Used in Mobile Communication Tested for Adverse Effects?

Based on available experimental data, it is believed that both beneficial and adverse health effects can be induced by NT MWs dependent on condition of exposure [1, 4, 6, 7, 11, 12, 14, 15, 20]. In contrast to thermal effects of MWs that can be described solely by SAR/PD, several other parameters and variables are important for the NT MW effects apart of SAR/PD.

One of the major growing public concerns is adverse health effect from mobile communication. Multiple sources of mobile communication result in chronic exposure of significant part of general population to MWs at nonthermal levels. Therefore, the ICNIRP safety standards, which are based on thermal effects in acute exposures cannot protect from the chronic exposures to NT MW from mobile communication [107].

Most of the real signals that are in use in mobile communication have not been tested so far. Very little research has been done with real signals and for durations and intermittences of exposure that are relevant to chronic exposures from mobile communication. In some studies, so-called "mobile communication-like" signals were studied that in fact were different from the real exposures in such important aspects as carrier frequency, modulation, polarization, duration, and intermittence. How relevant such studies to evaluation of adverse health effects from MWs of mobile communication is not known. For example, GSM users are exposed to MWs at different carrier frequencies during their talks. There are 124 different channels/frequencies, which are used in Europe for GSM900. They differ by 0.2 MHz in the frequency range from 890 MHz to 915 MHz. Mobile phone users are supplied by various frequencies from base stations depending on number of connected users. Frequency can be changed by base station during the same talk. GSM uses GMSK modulation (Gaussian Minimum Shift Keying). Contrary to GSM phones, UMTS mobile phones of the third generation (3G) use essentially QPSK (Quadrature Phase Shift Keying) modulation. 3G phones irradiate UMTS wide-band signals with the bandwidth of 5 MHz. UMTS MWs hypothetically may result in higher biological effects because of eventual "effective" frequency windows within bands.

We tested some of the real signals from GSM900 and UMTS mobile phones. Frequency-dependent effects of the NT MWs from GSM mobile phone on the DNA repair 53BP1/γ-H2AX foci and chromatin conformation in human lymphocytes were observed in replicated studies [39, 44, 54]. UMTS MWs induced significant adverse effects in human lymphocytes stronger or the same as effects of heat shock and GSM MWs at the carrier frequency of 915 MHz [54]. The results obtained were in line with our hypothesis that UMTS MWs may affect cells more efficiently than GSM MWs because of the nature of signal.

Urgent Needs and Further Perspectives

At present, a new situation arises when a significant part of population is exposed chronically (much longer than previously investigated durations of exposures) to NT MWs from different types of mobile communication including GSM and UMTS/3G phones and base stations, WLAN (Wireless Local Area Networks), WPAN (Wireless Personal Area Networks such as Bluetooth), DECT (Digital Enhanced (former European) Cordless Telecommunications) wireless phones. It cannot be excluded that some part of population, such as children, pregnant women, and groups of hypersensitive persons can be especially sensitive to the NT MW exposures. It is becoming more and more clear that the SAR concept that has been widely adopted for safety standards may not be useful for evaluation of health risks from MWs of mobile communication. How the role of other exposure parameters such as modulation, polarization, duration, and intermittence of exposure should be taken into account is an urgent question to solve. Answering this question would greatly benefit from the knowledge of the physical mechanisms of the NT MW effects.

The understanding of mechanisms for the NT MW effects is far away from comprehensive. Many questions remain to be addressed such as whether resonance effects of MWs depend on electromagnetic noise and SMF during exposure.

Beside fundamental importance, the development of comprehensive mechanisms is socially important for two main reasons. The first one is development of new medical treatment modalities using MWs. The second reason is accumulating evidence for adverse health effects of the NT MWs [11]. The adverse effects of MWs of mobile communications such as GSM and UMTS are of major concern in Europe because of increased exposures in many European countries to GSM/UMTS MWs from mobile phones and base stations. So far, most laboratory and epidemiological studies did not control important features of the NT MW effects as described above and therefore, only limited conclusion regarding health effects of MWs from mobile communication can be drawn from these studies.

It should be noted that one group of epidemiologists with long-lasting experience in studying relationship between mobile phone usage and cancer risk have consistently been concerned regarding importance of different MW signals and exposure durations [17–19, 108]. The Hardell group was the first epidemiological group in attempting to study separately the MW signals from cordless phones, analogue phones and digital phones. As a rule, analogue phones had the highest association with cancer risk. Cordless phones were associated with risk for brain tumors, acoustic neuroma, and T-cell lymphoma stronger or in the same degree as digital and analogue phones despite significantly lower SAR values were produced by cordless phones [17, 18, 20, 108]. This important result can be considered as

an independent conformation, at the epidemiological level, of the usually observed in specially designed in vitro and in vivo studies data that the NT MW effects depend not solely on SAR/PD but also on other parameters. It should be also noted that epidemiological data are controversial and methodological differences are a subject of debates between various research groups [20, 109]. However, from mechanistic point of view, the approach of the Hardell's group is more valid and the results of this group should be given priority as compared to other groups that ignore or minimize complex dependencies of the NT MW effects on several parameters/variables apart of SAR/PD [109].

The data about the effects of MWs at super low intensities and significant role of duration of exposure in these effects along with the data showing that adverse effects of NT MWs from GSM/UMTS mobile phones depend on carrier frequency and type of the MW signal suggest that MWs from base-stations/masts can also produce adverse effects at prolonged durations of exposure and encourage the mechanistic in vitro studies using real signals from base stations/masts. Further investigations with human primary cells under well controlled conditions of exposure, including all important parameters as described above, are urgently needed to elucidate possible adverse effects of MW signals that are currently used in wireless communication, especially in new technologies such as UMTS mobile telephony.

The dependence of adverse effects of NT MWs from GSM/UMTS mobile phones on carrier frequency and type of signal should be taken into account in settings of safety standards and in planning of in vivo and epidemiological studies. One important conclusion stemming from the available in vitro and in vivo studies is that epidemiological studies should not be given priority before proper design of these studies will be available as based on mechanistic understanding of the NT MW effects. This conclusion is based on 2 principle arguments. First, it is almost impossible to select control unexposed groups because whole population in many countries is exposed to wide range of MW signals from various sources such as mobile phones and base stations/masts of various kinds, WLAN, WPAN, DECT wireless phones and given that duration of exposure (must be at least 10 years for cancer latency period) may be more important for adverse health effects of NT MWs than PD/SAR. Second, the adverse effects of "detrimental" signals are masked because people are exposed to various signals/frequencies including noneffective or even hypothetically beneficial. From mechanistic point of view, current epidemiological studies are either inconclusive, if results are negative, or underestimate significantly the hazard of using specific signals, if results are positive.

The joining of efforts of scientific groups within national or international programs such as EU-programs is needed for mechanistic studies of the NT MW effects. To be based on the available science regarding biological action of NT MWs, this joining should involve scientists having long-lasting experience in studying the NT MW effects. Otherwise, misleading conclusions or inconclusive results may be expected.

Because NT MWs affect not only brain cells, but also blood cells [39, 44, 45, 69], skin and fibroblasts [63, 64, 103, 110], stem cells [96], reproductive organs [98, 110] the using of hands-free cannot minimize all adverse health effects. Possibilities to minimize the adverse effects of NT MWs using biophysical and biochemical approaches should be studied.

Identification of those types and frequency channels/bands for mobile communication, which do not affect human cells, and study of possibilities to minimize the adverse NT MW is urgently needed as the high priority task.

RNCNIRP proposed that guidelines for NT MWs should be developed further by studies based on the next priorities [13]. (1) Acute and chronic bioeffects of real MW signals as currently in use (GSM, UMTS/3G phones and base stations, etc.) should be tested in experiments with primary human cells and animals. (2) Studies with volunteers under controlled conditions of chronic exposures. Complains by phone users cannot be used for objective evaluation of health effects from mobile phones. There is a need for correlation of these complains with the data obtained in studies using the objective criteria. The data from the acute exposures of volunteers have very limited value because possible accumulation of effects during real chronic exposure is not evaluated. (3) Development of reliable and relevant methods to control personal exposures. (4) Epidemiological investigations of the postponed adverse health effects on various functions of organism and diseases including neurodegenerative diseases and cancer.

Conclusions

In conclusion, both beneficial and adverse health effects might stem from exposure to NT MWs depending on specific parameters of exposure. The NT effects of MWs would achieve wider acceptance if they could be explained by well-defined physical mechanisms. Knowledge of these mechanisms is necessary to evaluate biological significance of the NT MW exposure based on hard science but not on other issues including dismissing of the NT MW effects just because of their evident contradiction to the ICNIRP safety-exposure standards. In today's research, the most important task is to study these mechanisms. Most probably, the mechanisms of the NT MW effects must be based on quantum-mechanical approach and physics of non-equilibrium and nonlinear systems [5, 91, 111, 112].

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List of Abbreviations

anomalous viscosity time dependence (AVTD)
blood-brain barrier (BBB)
catalase (CAT)
Digital Enhanced (former European) Cordless Telecommunications (DECT)
circularly polarized (CP)
continuous wave (CW)
Digital Advanced Mobile Phone System (DAMPS)
discontinuous transmission (DTX)
electroencephalographic (EEG)
electromagnetic field (EMF)
embryonic stem (ES) cells
ethidium bromide (EtBr)
extremely low frequency (ELF)
Gaussian Minimum Shift Keying (GMSK)

ginkgo biloba (Gb)
Global System for Mobile Communication (GSM)
glutathione peroxidase (GSH-Px)
International Commission for Non-Ionizing Radiation Protection (ICNIRP)
linearly polarized (LP)
malondialdehyde (MDA)
micronucleus (MN) assay
microwaves (MWs)
N-acetyl-beta-d-glucosaminidase (NAG)
nitric oxide (NO)
nonthermal, NT
ornithine decarboxylase (ODC)
phorbol ester 12-myristate 13-acetate (PMA)
phosphorylated H2AX histone (γ-H2AX)
power density (PD)
regional cerebral blood flow (rCBF)
Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP)
specific absorption rate (SAR)
static magnetic field (SMF)
superoxide dismutase (SOD)
Time Division Multiple Access (TDMA)
tumor suppressor p53 binding protein 1 (53BP1)
ultraviolet (UV)
Universal Mobile Telecommunications System (UMTS)

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